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The effect of ulinastatin on hyperglycemia in patients undergoing hepatectomy

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ABSTRACT

Background: To identify the effect of ulinastatin (UTI) administration on stress-induced hyperglycemia and acute insulin (INS) resistance experienced by patients undergoing partial hepatectomy.

Methods: Forty-six patients undergoing partial hepatectomy were assigned randomly to the control group (group C) or UTI treatment group (group U). Six cases underwent partial hepatectomy but were not eligible for inclusion. The patients in group U had an intravenous infusion of a total amount of 5000 IU/kg UTI before the induction of anesthesia and at the start of surgery. The patients in group C were given an identical volume of physiological saline in the same manner. Blood samples for the measurement of interleukin-6, cortisol, INS, and glucagon were obtained. Fasting plasma glucose concentration was measured immediately before skin incision (T1), 20 min after the liver lesion was removed (T2), at the end of surgery (T3), as well as on the first (T4) and second mornings after partial hepatectomy (T5). The insulin sensitivity index (ISI) was calculated at these time points.

Results: The fasting plasma glucose concentration in group U was significantly lower than that in group C at all time points except for T1. In group U, the insulin sensitivity index was higher, and the levels of interleukin-6, cortisol, and INS were lower than that in group C ($P < 0.05$).

Conclusions: The data suggest that UTI administration improves perioperative hyperglycemia by inhibiting the inflammatory reaction, as well as excessive release of inflammatory factors, and improves INS resistance.

1. Introduction

Dysglycemia during the perioperative period refers to any disorder in the stability of glucose levels in serum. This includes diabetes-induced hyperglycemia in previously diagnosed or undiagnosed patients; impaired glucose tolerance; impaired fasting glucose; stress-induced hyperglycemia in nondiabetic patients; and hypoglycemia. It is very common in patients undergoing major surgical procedures. However, hyperglycemia is the most common pattern of dysglycemia in clinical practice.

Considerable attention has been paid to hyperglycemia because it is an early warning sign of a poor prognosis [1,2]. Several measures have been taken to avoid hyperglycemia in patients undergoing major surgery. However, the treatment strategy of hyperglycemia is controversial. A moderate target for glycemic control has not been determined, and the benefits and risks of intense glucose control

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by insulin (INS) in critically ill patients have been questioned [3,4].

Hyperglycemia refers to excess glucose in the blood, which means that glucose is not being metabolized appropriately. Hyperglycemia in major surgery usually involves hyperinsulinemia (i.e., cells are deconditioned to the INS stimulus and do not take up glucose very well). During such a condition, INS administration is not the best way to regulate the unstable level of glucose in blood because INS resistance occurs. Recent studies have indicated that perioperative hyperglycemia is, in general, related to the following conditions: preoperative metabolic condition; dysregulation of the neuroendocrine system; release of cytokines subsequent to the stress response; acute INS resistance; specific features of the surgical procedure, and perioperative management [5,6]. Therefore, theoretically, any intervention that regulates the neuroendocrine stress response and release of cytokines perioperatively can also modulate the consequent dysglycemia and mitigate perioperative hyperglycemia. Similar effects of propofol or opioids have been reported [7].

Hepatectomy is very different from other types of surgery. It involves very complicated occlusion and reopening of vessels, manipulation of the first and second hepatic portal vein, and the inferior vena cava. These procedures can contribute to ischemia–reperfusion injury to liver cells and the release of many inflammatory factors. These factors serve as a strong stress response that facilitates hyperglycemia during surgery.

Ulinastatin (UTI) is a broad-spectrum protease inhibitor. It is a type of glycoprotein separated and purified from human urine. It has been used widely in patients with acute inflammatory disorders such as acute pancreatitis, shock, systemic inflammatory reaction syndrome, and multiple organ dysfunction syndrome. *In vitro* experiments have demonstrated that UTI ameliorates ischemia–reperfusion injury by inhibiting neutrophil accumulation in the postischemic liver [8]. Recent *in vivo* and *in vitro* studies have also indicated that UTI administration can inhibit the additional expression of inflammatory cytokines such as tumor necrosis factor (TNF-α), interleukin (IL)-2 and IL-8 (which play important parts in dysglycemia), impairment of the blood–brain barrier, as well as postoperative cognitive dysfunction [9–13]. Recent research has also suggested that UTI could be a useful marker of chronic inflammatory conditions in patients with type-1 or type-2 diabetes [14]. However, treatment of perioperative hyperglycemia by UTI administration has not been reported.

We hypothesized that UTI could ameliorate perioperative hyperglycemia. We obtained blood samples through central venous catheters that had been inserted via the right jugular vein after general anesthesia (GA) at several fixed time points or events during and after hepatectomy. Fasting plasma glucose (FPG), interleukin-6 (IL-6), cortisol (COR), INS, and glucagon (GLU) were measured in these blood samples. The insulin sensitivity index (ISI) was calculated to evaluate the benefit of UTI for controlling perioperative hyperglycemia.

2. Materials and methods

The study protocol was approved by the Ethics Committee of Guangdong General Hospital (Guangdong Academy of Medical Sciences) and registered in the Chinese Clinical Trial Registry (Registration number ChiCTR-TRC-13003829). Written informed consent was obtained from each patient.

Forty-six American Society of Anesthesiologists (ASA) I–II patients for laparotomy hepatectomy from October 2012–May 2013 were enrolled. The inclusion criteria were (i) Child–Pugh score $\leq$10 and (ii) no metastasis to other organs. The exclusion criteria were (i) abnormal findings on electrocardiography or chest radiographs; (ii) cardiac or pulmonary insufficiency; (iii) severe renal dysfunction; (iv) preoperative hemoglobin level $<$100 g/L; (vi) allergies; (vii) history of drug abuse; and (viii) infusion of glucose-containing liquid $<$8 h before surgery. Patients who had one of the following severe complications or events were also excluded as follows: (i) cardiovascular events; (ii) allergic shock; (iii) reoperation; (iv) hepatic failure; and (v) postoperative INS therapy. Patients were assigned randomly (by a computer-derived random number sequence) to two groups to intravenous infusion of 2500 IU/kg UTI (UTI treatment group or group U) or saline (control group or group C) at the beginning of anesthesia and surgery, respectively. Double-blind processing was carried out. That is, study drugs were dissolved in 20 mL physiological (0.9%) saline or only 0.9% saline with the same type of syringe, and markers were prepared according to the randomized groups by a person who did not take part in sample measurements or postoperative follow-up. The attending anesthesiologist and data collector were blinded to the infusion drug.

The general anesthetic method and perioperative management were standardized. Five-lead electrocardiography, noninvasive blood pressure, end-tidal PCo_2 ($EtCO_2$), heart rate (HR), and pulse oximetry (SpO_2) were recorded. A central venous catheter was placed in the right internal jugular vein for continuous monitoring of central venous pressure. An electroencephalography monitor version 4.3 (Narcotrend; MT MonitorTechnik GmbH, Bad Bramstedt, Germany) was connected to patients for assessing anesthetic depth. Atropine (0.01 mg/kg, intravenously) and midazolam (3 mg, intravenously) were administered to all patients 30 min before surgery. GA was induced with 1.0 mg/kg propofol and 4.0–5.5 ng/mL remifentanil by target-controlled infusion followed by injection with 0.6 mg/kg cisatracurium to facilitate tracheal intubation. GA was maintained with target-controlled infusion of remifentanil and sevoflurane inhalation in O_2 (50%–100%), and the depth of anesthesia with the Narcotrend index at 20–46 (stage D2–E1) was maintained. Intermittent positive-pressure ventilation with an adequate tidal volume to maintain an $EtCO_2$ of 36–40 mm Hg was maintained at a fresh gas flow of 2 L/min. Extra fentanyl and muscle-relaxation agents were infused intravenous according to need.

On the premise of a stable depth of anesthesia, fluctuation of mean arterial blood pressure (MAP) $<$20% or HR $<$30% to baseline was treated by adjusting the end-tidal concentration of sevoflurane and the infusion target of remifentanil or intravenous fluid speed. As adverse hemodynamic responses occurred (defined as fluctuation of MAP $>$20% or HR $>$30% to baseline), vasopressors (dopamine, norepinephrine, or glonoin) were infused to maintain hemodynamic stability followed by procedures to find out the pathogenesis of the events and initiate therapy. Bradycardia (HR $<$45 bpm) was treated by 0.01 mg/kg atropine. Hydroxyethyl starch solution (6%) (130/

0.4) and Plasma Lyte A (Shanghai Baxter Healthcare Ltd, Shanghai, China) were used for fluid therapy, and blood products were administered if required.

All patients received intravenous analgesia postoperatively using a defined strategy. That is, fentanyl (1 μg/kg) + flurbiprofen (80 mg) were infused as the first dose as soon as the skin was sutured. Doses of 18 μg/kg fentanyl, 200 mg flurbiprofen, and 40 mg azasetron were mixed and diluted with normal saline up to 100 mL. This mixture was administered at 2 mL/h and maintained for 50 h using a disposable pump.

To measure levels of FPG, IL-6, COR, INS, and GLU, samples of venous blood were obtained before skin incision (T1), 20 min after the liver lesion was removed (T2), at the end of the hepatectomy (T3), as well as on the first (T4) and second mornings after hepatectomy (T5). Blood samples (5 mL) were centrifuged at 3000 rpm for 10 min at −4°C. Serum was stored at −80°C. FPG levels were measured immediately using the ABL800 FLEX blood gas analyzer (Radiometer, Copenhagen, Denmark); IL-6 levels were measured using an enzyme-linked immunosorbent assay kit (ExCell Biology, Shanghai, China); COR, INS, and GLU levels were measured using a radioimmunoassay kit (Beijing North Institute of Biological Technology, Beijing, China). The ISI was calculated according to the method of Li and Pan [15] using the formula:

$$ISI = 1/(FINS \times FPG)$$

The natural logarithm of the ISI is used for evaluating INS sensitivity, that is, the smaller the value, the worse the impairment of INS sensitivity.

Hyperglycemia was defined as an FPG level >10 mmol/L at any time point. The prevalence of hyperglycemia in the two groups was calculated.

2.1. Statistical analyses

Statistical analyses were carried out using SPSS version 20.0 (SPSS, Chicago, IL). The sample size in this prospective study was calculated on the basis of our pilot study with $\alpha = 0.05$ and $\beta = 0.80$: 18 patients were needed in each group. Numerical data are the mean ± standard error of the mean. Categorical data are presented as the component ratio. Numerical data, including concentrations of FPG, IL-6, COR, INS, and GLU as well as the ISI between the two groups, were analyzed using the Student *t*-test. Intragroup numerical data were analyzed using repeated measures analysis of variance. The prevalence of hyperglycemia between the two groups was analyzed using the Pearson χ^2 test. $P < 0.05$ was considered significant.

3. Results

Forty patients out of 46 candidates completed the study. There were no significant differences in demographic data between groups ($P > 0.05$; Table). There were no significant differences in HR, MAP, $EtCO_2$, SpO_2, and Nacotrend index during hepatectomy between the two groups ($P > 0.05$). No significant differences in levels of FPG, IL-6, COR, INS, and GLU or the ISI between groups were found at T1 ($P > 0.05$).

Table – Demographic data.

Demographic data	Group C	Group U
Age (y)	51 ± 11	51 ± 10
M/F (*n*)	15/5	16/4
Weight (kg)	58.5 ± 7.6	59.4 ± 8.1
BMI (kg/m^2)	22.9 ± 2.0	23.0 ± 2.2
Child–Pugh grade A/B (*n*)	17/3	17/3
Duration of surgery (min)	200 ± 35	206 ± 27
Blood loss (mL)	425 (200–625)	400 (100–600)

BMI = body mass index.
No statistical significances were observed between the two groups.
Data are the mean ± SD, median, and range or number of patients.

FPG concentration in the two groups showed a similar trend. However, FPG concentration increased as hepatectomy proceeded to a maximum at T2–T3 and then declined after the procedure ($P < 0.05$). In group U, FPG concentration was significantly lower at any time point except T1 when compared with group C ($P < 0.05$). FPG concentration (in millimole per liter) in group U showed a difference of 2.64 ± 0.60 at T2 (95% confidence interval 1.41–3.86), 2.20 ± 0.47 at T3 (1.26–3.14), 1.83 ± 0.73 at T4 (0.35–3.30), and 1.85 ± 0.43 at T5 (0.98–2.70) compared with that in group C (FigureA).

To determine acute INS resistance between the two groups, the ISI was calculated (FigureB). The ISI decreased during and after hepatectomy compared with its baseline level (T1) in all groups ($P < 0.05$), but the extent of the decrease in group U was much lower at T2–T5 compared with that in group C ($P < 0.05$). The ISI in group U showed a difference of −1.10 ± 0.26 at T2 (95% confidence interval −0.57 to −1.64), −0.97 ± 0.28 at T3 (−0.40 to −1.54), −0.71 ± 0.32 at T4 (−0.06 to −1.35), and −1.40 ± 0.24 at T5 (−0.92 to −1.89) compared with that in group C.

To explain the changes in FPG concentration between the two groups, concentrations of INS and GLU were measured at identical points. For INS, the concentrations in the patients of the two groups showed an upward trend during hepatectomy and reached a peak at T4, then fell dramatically at T5 ($P < 0.05$; FigureC). Compared with group C, the concentration of INS was significantly lower in group U ($P < 0.05$) at T2–T3 and T5, whereas the difference in GLU level between the two groups was not significant at any time point ($P > 0.05$, FigureD).

To describe the stress and inflammation reactions, levels of COR and IL-6 were measured between the two groups. The concentration of COR increased during hepatectomy and fell after surgery, and the difference between the two groups was significant ($P < 0.05$) at T2–T5 (FigureE). The concentration of IL-6 increased during hepatectomy and reached a peak at T4 (compared with T1, $P < 0.05$) in the two groups. However, group U had a lower IL-6 concentration than that in group C ($P < 0.05$) at T2–T3 (FigureF).

Group U showed a lower prevalence of hyperglycemia compared with group C (5% *versus* 45%, $\chi^2 = 8.53$, $P < 0.01$) when we defined perioperative hyperglycemia to be 10 mmol/L. The prevalence of postoperative complications (e.g., fever and poor wound healing) was not significantly different between the two groups ($P > 0.05$). The other postoperative indices (including period of hospitalization, neutrophil number, and level of aspartate transaminase) were also not significantly different between the two groups ($P > 0.05$).

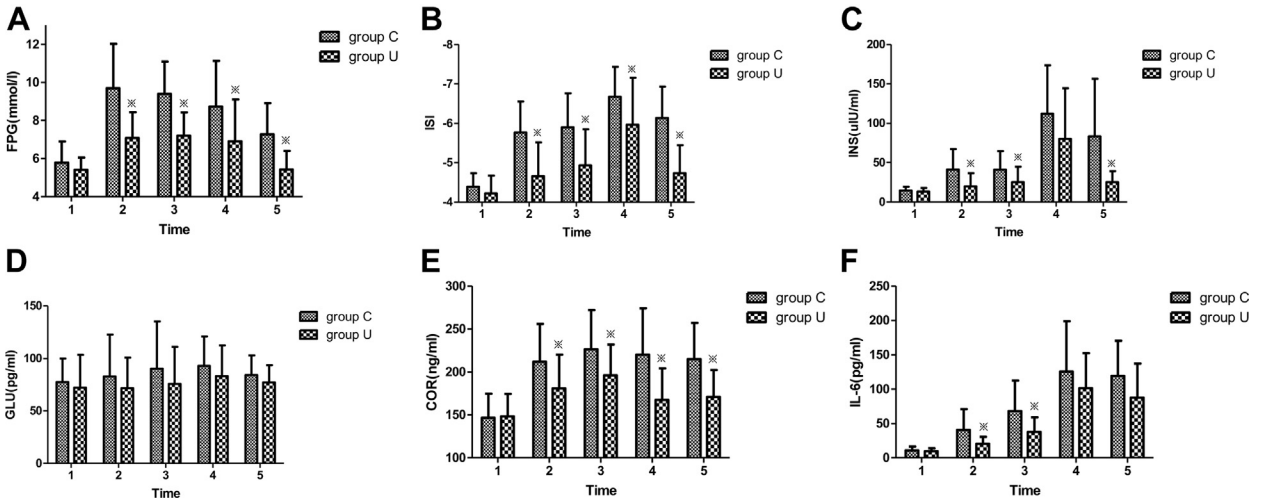

Figure – Effect of UTI on stress hyperglycemia and acute INS resistance. (A) The FPG level in the two groups showed a similar trend during and after partial hepatectomy. The FPG level was significantly lower in group U compared with that in group C. (B) UTI treatment ameliorated the impairment of INS sensitivity during and after partial hepatectomy. (C) Effect of UTI on INS level. (D) The difference in GLU level between groups was not significant at any time point. (E) Effect of UTI on COR level. (F) Effect of UTI on IL-6 level. T1: before skin incision; T2: 20 min after removal of the liver lesion; T3: end of surgery, T4: first morning after surgery, and T5: second morning after surgery ※$P < 0.05$.

4. Discussion

UTI at 300,000 IU per day has been found to be the recommended dose for acute circulatory failure in clinical studies [16]. Another study in Japan demonstrated that UTI 6000 IU/kg is the maximum safe dose [17]. In the present study, total administration of 5000 IU/kg UTI was studied.

We observed that UTI administration clearly attenuated the severity and duration of perioperative hyperglycemia. The FPG concentration in group U was lower during and after hepatectomy than that in group C, and was then restored to its preoperative level at the second morning after surgery. A potential mechanism may be the modulation of the stress response and release of inflammatory cytokines by UTI.

The variation in COR level is closely associated with the degree of trauma. The present study demonstrated that the range of increase of the COR level in patients who underwent UTI treatment during and after hepatectomy was significantly lower than that in group C. This finding suggested that UTI could effectively reduce the stress response arising from surgical trauma. Activation of the hypothalamus–pituitary–adrenal cortex axis plays a pivotal part in the perioperative stress response. COR (whose secretion increases on intraoperative stress) can (together with adrenaline and GLU) trigger hyperglycemia by targeting enzyme substrates, taking up gluconeogenic precursors in the liver, boosting the mobilization of glycogen stores, facilitating glucose release in the liver, promoting dysplasia and mobilization of fasting glycogen reserves, and prompting the liver to release glucose and minimizing entry of glucose into the liver [6].

To investigate pancreatic endocrine function during the perioperative period, the INS:GLU ratio was calculated according to the groups. In this way, the relationship between the UTI gradient and the pancreatic function could be assessed. Theoretically, GLU can promote glycogenolysis and gluconeogenesis under stress, but GLU secretion did not show obvious changes between groups. This unexpected finding suggested that GLU did not contribute much to perioperative hyperglycemia. According to one study, this phenomenon might be related to reflex inhibition of hyperglycemia against GLU secretion [18]. INS is the only hormone that can lower blood glucose levels. INS secretion can be triggered by an increased concentration of FPG but is not completely parallel to the FPG level, and other factors such as INS resistance are also involved [3]. In the present study, INS secretion in the two groups peaked on the first day after hepatectomy. However, the INS concentration in group U was significantly lower than that in group C, which was due to differences in the FPG level and INS resistance (i.e., the change in the ISI) between groups.

In the present study, UTI was administered twice separately to ensure an effective plasma concentration throughout surgery as far as possible because of its short half-life *in vivo*. With the plasma concentration decreasing after surgery, blood-glucose regulation by UTI is usually considered to be restricted to the intraoperative period rather than the postoperative period. However, the postoperative differences in FPG levels in the two groups could have been attributable to the beneficial amelioration of INS resistance, which might contribute to a reduction in surgical trauma by UTI.

Considering the fact that it is most noticeable on the first postoperative day [3], INS resistance has a critical role in sustaining postoperative hyperglycemia, along with ceased surgical stimulation and recovered hormone levels related to stress after surgery. Hyperinsulinemic euglycemic clamp technique (HECT) is considered as the most authoritative method to evaluate INS sensitivity. However, HECT is an expensive and time-consuming process, which constrains its

application. Li and Pan [15] reported a simple index, which is fit for the evaluation of the ISI in Chinese population because of its significant correlation with the ISI determined by HECT. In the present study, intraoperative and postoperative ISI values calculated by the way of Li and Pan were higher in group U than those in group C, which suggested that the impairment in INS sensitivity was ameliorated by UTI. To investigate the relationship between inflammatory factors and INS resistance, plasma levels of IL-6 were measured. However, as a cytokine with multiple functions, the TNF-α concentration is influenced by several factors. Most of our patients had malignant hepatic tumors, and TNF-α levels in such patients are higher than those of healthy subjects [19]. For this reason, the TNF-α concentration was not studied.

It has been reported that UTI can restrain the excessive release of inflammatory factors such as TNF-α and IL-6 [11,12]. We also found that the IL-6 concentration in group U was significantly lower than that in group C except for the second morning after surgery. TNF-α and IL-6 are the main inflammatory factors released after tissue damage and are involved in the development of INS resistance [3]. TNF-α and IL-6 have been shown to induce serine phosphorylation of INS receptor substrate-1, which inhibits the normal tyrosine phosphorylation of receptor substrate-1, by which cellular signal transmission is suppressed. Furthermore, TNF-α and IL-6 can enhance lipolysis to increase the amount of free fatty acids and inhibit glucose transporters [20]. Ultimately, INS resistance occurs.

As mentioned previously, a moderate target for glycemic control has not been determined. Some authors have suggested that it would be prudent to maintain glucose levels <10 mmol/L in the perioperative period until further (more specific) data are accumulated [3]. Several investigators have defined conventional control target glucose levels during the perioperative period to be ≤10 mmol/L [21,22]. In the present study, hyperglycemia was defined as FPG level >10 mmol/L at any time point. The prevalence of hyperglycemia was clearly lower in group U compared with that in group C, which suggested that UTI could reduce the demand for glucose control by INS. At the same time, no case of low blood glucose was observed in any patient. With the decreasing demand of glucose control, the risk of hypoglycemia and necessity of frequent monitoring of blood glucose also decreased.

This study has some limitations. Only one dose of UTI was administered intraoperatively. The question of whether UTI has a dose-dependent effect on perioperative hyperglycemia is beyond the scope of the present study. Also, because of objective condition restrictions, there were unparalleled interferences of blood loss and different surgeons in each patient.

5. Conclusions

In conclusion, the present study suggested that UTI administration improves perioperative hyperglycemia by inhibiting the inflammatory reaction as well as excessive release of inflammatory factors and improves INS resistance. Further clinical studies examining various doses and prolongation of UTI for perioperative hyperglycemia are warranted.

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Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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